

REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as proposed to be amended, pursuant to and consistent with 37 C.F.R. § 1.116, are respectfully requested in light of the remarks that follow.

The foregoing amendment seeks to add new Claims 64-85. New Claim 64 represents a combination of the features of Claim 21 and the features of Claim 29, i.e., its method is limited to at least one of the specific glucosylated hydroxystilbene compounds named in Claim 29. New Claim 65 combines the features of Claims 45 and 29; previously presented Claim 29, drawn to the same subject matter, but in dependent form, has accordingly been proposed to be canceled as redundant. New dependent Claims 66 and 67 parallel Claims 46 and 47, respectively. New Claim 68 combines the features of Claims 48 and 29. New dependent Claims 69 and 70 parallel Claims 46 and 47, respectively. New Claim 71 combines the features of Claims 51 and 56. New dependent Claims 72 and 73 parallel Claims 62 and 63, respectively. New Claim 74 is based on Claim 21, but is limited to a method for combating signs of aging of the hair follicles. New dependent Claims 75 and 76 parallel Claims 46 and 47, respectively. New Claim 77 is based on Claim 48, but is limited to a method for combating signs of aging of the hair follicles. New dependent Claims 78 and 79 parallel Claims 46 and 47. New Claim 80 is based on Claim 21 but is limited to a method for combating signs of aging of the hair follicles; Claim 80 further includes the features of Claim 29, that is, its method is limited to at least one of the glucosylated hydroxystilbene compounds named in Claim 29. New dependent Claims 81 and 82 parallel Claims 62 and 63, respectively. New Claim 83 is based on Claim 48 but is limited to a method for combating signs of aging of the hair

follicles; Claim 83 further includes the features of Claim 29 and thus its method is limited to at least one of the glucosylated hydroxystilbene compounds named in Claim 29. New dependent Claims 84 and 85 parallel Claims 62 and 63, respectively.

It is apparent from the foregoing that the new claims do not raise any new matter issues. Upon entry of the foregoing amendment, Claims 21-25, 27, 28, 30-34 and 45-85 will be in this application.

The acknowledgment of the claim for foreign priority and of the certified copy of the priority document is noted, with appreciation.

The withdrawal of the 35 U.S.C. § 112, second paragraph, rejection is also noted, with appreciation.

Claims 21-22, 24-25, 29-31, 45, 48-49 and 51-58 have been rejected under 35 U.S.C. § 102(b) as purportedly anticipated by Pruche et al. FR 2787319, which is equivalent to Pruche et al. U.S. Patent No. 6,409,772B2, for reasons of record. It is the Examiner's position that Pruche et al. discloses a method of applying a composition comprising a particular compound of formula (I), 4',5-dihydroxystilbene-3-O- β -D-glucoside (also a particular compound herein), a physiologically acceptable medium and additives, to keratinous materials such as hair, as well as to the skin, e.g., dyeing of the skin and dyeing hair. Pruche et al. disclose using their compound of formula (I) in a ready-to-use dye composition in an amount of 0.01 to 10% by weight relative to the total weight of the ready-to-use dye composition.

Applicants continue to maintain that the Pruche et al. patents do not anticipate applicants' invention, and that none of the claims in this application following entry of this amendment is anticipated thereby. It is submitted that the Examiner is extracting from the Pruche et al. patents those teachings which suit his purpose, without taking

into account what Pruche et al. as a whole teach to one of ordinary skill in the art. At the same time, the Examiner appears to be ignoring the fact that applicants are claiming methods, not compositions, and that applicants' methods can differ in many respects from those of Pruche et al.

Looking at Pruche et al. U.S. Patent No. 6,409,772B2, it is first noted that, while the specific compound named by the Examiner is in fact named in the '772 patent, the patent encompasses non-glucosylated hydroxystilbenes and glucosylated hydroxystilbenes; indeed the only exemplification therein is of resveratrol, which is a non-glucosylated hydroxystilbene. The specific compound singled out by the Examiner has been singled out only because it can also be employed in applicants' methods; it has not been singled out by Pruche et al.

Even more significantly, it is clear from the Pruche et al. patents that the hydroxystilbenes are used therein as oxidation dye precursors in dye compositions. As oxidation dye precursors, these compounds are combined with an oxidant, that is, the precursor and the oxidant react with each other in order to achieve the dyeing result. Without such an oxidant, no oxidation process in fact occurs, and thus no dyeing results.

Thus, a fair reading of the Pruche et al. patents leads one of ordinary skill to conclude that the Pruche et al. hydroxystilbenes can be used with an oxidant to dye keratin fibers/hair. (It is not seen that a method of dyeing the skin is disclosed and indeed this is believed to be undesirable, as a person having his or her hair dyed does not want his or her scalp to also be colored!) The Pruche et al. patents do not suggest how the hydroxystilbenes could function to dye skin or hair unless they are combined with an oxidant. All the Pruche et al. examples include an oxidant

(laccase or tyrosinase). And the prior art composition comprising an oxidant is not an anti-aging composition but a dyeing product. Indeed, it is well-known that usual anti-aging compounds are anti-oxidants and that an oxidant would counteract the anti-aging effect. Clearly, one of ordinary skill would not expect Pruche et al.'s hydroxystilbenes combined with an oxidant to dye a support, in particular keratin substances, to nevertheless exert an anti-oxidant anti-aging effect. Applicants methods thus are clearly not inherent in what the Pruche et al. patents teach. As pointed out previously, "to establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Robertson*, 169 F.3d 743, 49 U.S.P.Q.2d 1949, 1950-51 (Fed. Cir. 1999). There is no case for inherency here.

Applicants' claims provide for combating signs of cutaneous aging or aging of the hair follicles, or for increasing skin radiance or smoothing the skin, or for lessening the appearance of wrinkles or fine lines, or for stimulating epidermal renewal. Pruche et al.'s dyeing methods, which to accomplish dyeing must include an oxidant, do not contain effective amounts of their hydroxystilbenes to accomplish applicants' methods because Pruche et al.'s oxidant, essential for the dyeing purpose, would counteract any anti-oxidant anti-aging effect that could occur in the absence of oxidant.

For at least the reasons set forth above, it is submitted that all of applicants' claims are free of the 35 U.S.C. § 102(b) rejection as anticipated by Pruche et al.

Claims 21-25, 27-34, 45, and 48-60 stand rejected under 35 U.S.C. § 102(e) as purportedly anticipated by Pezzuto et al. (WO 01/30336). This rejection is respectfully traversed. Indeed all of applicants' claims as set forth above are believed to be free of this rejection.

The Examiner notes that "Pezzuto et al. (WO 01/30336) discloses a method for treating or preventing skin conditions such as those associated with sun damages and natural aging comprising topically administering a composition comprising a topical carrier (emulsifiers, solubilizers, emollients, preservatives, water) and a prodrug of resveratrol such as cis or trans resveratrol glucosides". The Examiner also indicates that "Pezzuto et al. teach resveratrol and its glucosides are art equivalents".

Applicants admitted previously that Pezzuto et al. disclose the use of resveratrol glucoside among a variety of other derivatives of resveratrol:

Generally, the active agent will be cis-resveratrol, trans-resveratrol, or a complex in which one or more of the compounds hydroxyl groups are conjugated to a mono- or di-saccharide, e.g., cis-resveratrol glucoside, trans-resveratrol glucoside, etc.

Further, applicants admitted previously that Pezzuto et al. preferred cis-resveratrol glucoside and trans-resveratrol glucoside among derivatives of resveratrol. Applicants never admitted that these particular derivatives were particularly preferred by Pezzuto et al. for use in Pezzuto et al.'s method, and the Examiner is mistaken in saying so. In point of fact, the glucosylated hydroxystilbenes of the present invention are not explicitly disclosed, and their use in cosmetic compositions and their efficiency or advantages over resveratrol itself are not explicitly disclosed either by Pezzuto et al. Pezzuto et al. exemplify and thus clearly prefer only resveratrol itself. Moreover, applicants have shown previously

that glucosylated hydroxystilbenes are not art recognized equivalents of resveratrol in terms of anti-oxidant properties; see previously cited Teguo et al. Based on Teguo et al. and Pezzuto et al., one of ordinary skill would expect Pezzuto et al.'s invention to be successful for resveratrol, but would not have a reasonable expectation of success for glucosylated hydroxystilbenes in Pezzuto et al.'s invention.

Specific glucosylated hydroxystilbenes named in the present claims, such as Claims 64-73 and 80-85 are not even named by Pezzuto et al., much less their improved properties in terms of stability and solubility over resveratrol itself. Moreover, there is not a scintilla of a suggestion in Pezzuto et al. of combating signs of the aging of hair follicles, which is claimed in many of applicants' claims; indeed, Claims 74-85 are solely directed to that subject matter, among which Claims 80-85 are additionally directed to applying at least one of a group of specifically named glucosylated hydroxystilbenes. For these reasons, Claims 64-85 are directed to subject matter which is in no way anticipated by or obvious from Pezzuto et al.

Claims 21-25, 27-34, and 45-63 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Carson et al. (WO 99/047047), Pezzuto et al. (WO 01/30336) and Teguo et al., all of record. The Examiner argues that Carson et al. disclose that resveratrol is useful in a method of inhibiting the proliferation of keratinocytes and stimulating their differentiation and improving skin. Further, the Examiner asserts that Carson et al. disclose that cosmetic compositions containing grape extracts are known in the art, that Pezzuto et al. teach resveratrol and its glucosides are art equivalents and that Teguo et al. teach E and Z piceid, among others, are found in *Vitis vinifera* and *Polygonum cuspidatum* root. Thus, the Examiner concludes it

would have been obvious to use grape extracts to treat and improve skin. This rejection, to the extent that it applies to the claims as amended, is respectfully traversed.

Carson et al. teach that resveratrol, a phytoestrogen, is useful in methods of inhibiting the proliferation of keratinocytes and stimulating their differentiation, improving the appearance of wrinkled, lined, dry, flaky, aged or photodamaged skin, improving skin thickness, elasticity, flexibility, radiance, glow and plumpness, according to the abstract and Claims 3 and 4. These methods require an amount of from 0.00002 to 10 wt.% of resveratrol, according to Carson et al. Carson et al. also teach that resveratrol is found in a variety of common edible plants, including red grapes. Page 4, line 1 to page 5, line 9 discuss the art known to Carson et al. The only disclosure noted by Carson et al. that mentions any amount of grape to be used for cosmetic purposes is JP 06336421, which teaches the presence of 0.5% of grape extract in its compositions. Carson et al. calculate that this would have a resveratrol concentration of 0.33 micromolar or 0.0000075 wt.%, far below the amount deemed effective by Carson et al.

Although Carson et al. teach that resveratrol can be found in wine and grapes, they do not teach that wine or grape extracts can be applied to the skin to carry out their claimed methods. They teach only that the compound resveratrol itself can be used in their methods. Most importantly, they do not teach that an effective amount of any derivative of resveratrol, much less a glucosylated resveratrol, could be used topically to improve the skin conditions according to their invention. Indeed, the Carson et al. reference is silent as to the possibility of using glucosylated resveratrol or any other glucosylated hydroxystilbene in their method.

The teachings of Pezzuto et al. have been discussed above. Pezzuto et al. as pointed out above, exemplify only resveratrol; moreover, of glucosylated derivatives, only those of cis- and trans-resveratrol are even named in the WO publication. Further, the Examiner's conclusion from Pezzuto et al. that all glucosylated hydroxystilbenes are equivalents of resveratrol is contradicted by Tegu et al.

The Tegu et al. publication reports that the glucosylated hydroxystilbenes tested (one of which was piceid) have anti-oxidant activities far inferior to the non-glucosylated hydroxystilbenes tested (one of which was resveratrol). Indeed, the reduction was seven times in the case of (E)-piceid (Compound 3) versus (E)-resveratrol. This is a teaching away from use of glucosylated resveratrol in place of non-glucosylated resveratrol as equivalents. In fact, in light of Tegu et al., applicants' finding that glucosylated hydroxystilbenes can be used to good effect in methods for improving skin conditions as claimed herein is quite surprising. Even more surprising is the advantageous nature of the glucosylated hydroxystilbenes over resveratrol shown in the specification and the Exhibits filed December 12, 2003.

Independent Claims 21, 22, 23, 24, 25, and 45 as well as the new independent claims 64, 65, 74, 80 recite the application of a composition consisting of (i) at least one glucosylated hydroxystilbene compound as the active principle, (ii) one or more usual cosmetic or pharmaceutical additives, and (iii) a physiologically acceptable medium therefor. Thus, the presently claimed invention does not encompass methods using compositions comprising non-glucosylated hydroxystilbenes as disclosed in the Carson et al. and, in particular, resveratrol or grape extract comprising a non-glucosylated form of resveratrol. In this regard,

applicants note that Claims 48-63, 68-73, 77-79 and 83-85 exclude an effective amount of non-glucosylated hydroxystilbene and thus, are also believed to be unobvious over the cited publications. Claims 64-85 are particularly remote from the art.

Moreover, it is not seen where the features of dependent claims requiring the presence of a glucosidase activator have been suggested by the art of record or pointed out by the Examiner.

It is abundantly clear that applicants' method is not disclosed or suggested by the cited art, taken separately or in combination. Certainly, the prior art references suggest no advantage to combining and modifying them to arrive at applicants' invention. The prior art itself must suggest the reason to combine them (*In re Sernaker*, 217 U.S.P.Q. 1) and indeed it does not. There simply is no basis for combining the cited references, for there is not even an allusion in any one of them for such combination. *United Merchants, etc. v. Ladd*, 139 U.S.P.Q. 199. Further, where references are combined, it should be considered whether those references suggest doing what applicants did. *In re Gruskin*, 110 U.S.P.Q. 288. The references relied upon here in no way meet that burden. Indeed, the references are silent as to a possible combination and, as was succinctly stated in *In re Burt & Walter*, 148 U.S.P.Q. 548, "Silence in a reference is hardly a proper substitute for an adequate disclosure of facts upon which a conclusion of obviousness may justifiably follow." Also in point as regards the references separately or in combination is *In re Wesslau*, 147 U.S.P.Q. 391, in which the Court stated:

It is impermissible within the framework of Section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full

appreciation of what such a reference fairly suggests to one of ordinary skill in the art.

In fact, it is only with the benefit of hindsight that one could arrive at applicants' invention and, as the CAFC succinctly put it in *Orthopedic Equipment Co., Inc. v. United States*, 217 U.S.P.Q 193:

It is wrong to use the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit. Monday morning quarterbacking is quite improper when resolving the question of non-obviousness in a court of law.

When fairly viewed, there is no question but that the cited references simply fail to teach or suggest applicants' invention.

It is clear that the references, separately or in combination, do not suggest using glucosylated hydroxystilbenes in the methods claimed herein. In the case of resveratrol and glucosylated resveratrol, previously cited Waterhouse et al show that grape extracts can contain both of these derivatives. Waterhouse et al. also show, however, that grape extracts vary greatly in their content and that extracts can be obtained which contain no measurable non-glucosylated hydroxystilbenes while other extracts can be obtained which contain no measurable glucosylated hydroxystilbenes. Thus, applicants' method can be readily carried out without using the Carson et al. method which requires resveratrol, even when applicants' glucosylated hydroxystilbenes are derived from wine. It is not applicants' intention to apply the non-glucosylated form in their invention; rather, it is applicants' intention, as discussed in the specification, to use glucosylated hydroxystilbenes, which applicants have found can be converted in the skin or hair follicles to the non-glucosylated hydroxystilbenes and which thus avoid the disadvantages of applying

the non-glucosylated hydroxystilbenes themselves directly (also detailed in the specification). The fact that the glucosylated form is converted into the non-glucosylated form in the skin or hair is the discovery of the present inventors that makes the instantly claimed method possible and avoids the disadvantage of direct application of the non-glucosylated compounds.

Moreover, applicants again submit that the presently claimed invention conveys special advantages in using the glucosylated form of hydroxystilbenes for treating and improving the skin. As discussed in the specification on page 2, lines 21-25 and page 3, lines 1-6, applicants have surprisingly found that glucosylated hydroxystilbenes can be converted in the skin or hair follicles to non-glucosylated hydroxystilbenes, which enables avoiding the disadvantages (e.g., decreased solubility and stability) of applying non-glucosylated hydroxystilbenes directly.

Applicants again submit that none of the cited publications either separately or in combination, discloses or suggests using glucosylated hydroxystilbenes as the active principle as in the presently claimed invention, nor is there any motivation to combine the cited publications.

Applicants respectfully submit that the presently claimed invention also possesses surprising and unexpected results which confirm its nonobviousness. That is, the presently claimed invention discloses unexpected results and advantages for the use of glycosylated hydroxystilbene. First, the present specification discloses that glucosylated hydroxystilbene is slowly hydrolyzed by glycosidases which are naturally secreted by the skin or the hair follicles, thereby releasing the active agent, i.e., the non-glucosylated hydroxystilbene. This is

evidenced by the fact that the release can be enhanced in a dose-dependent manner by glucosidase activators.

The present specification also provides evidence that the glucosylated hydroxystilbenes are more stable. This is demonstrated in Example 1. In the presence of tyrosinase, which is a polyphenol oxidase, resveratrol is slowly released, indicating a resistance of the glucosylated derivative against oxidation. This unexpected advantage was further confirmed by Regev-Shoshani et al. (*Biochem. J.*, 374:157-163 (2003), provided previously Exhibit A). See table 3 and p. 160, § Tyrosinase activity towards resveratrol and its derivatives.

Finally, glucosylated hydroxystilbenes exhibit better solubility in aqueous medium. The cited publications do not disclose or suggest any of the advantages of the glucosylated hydroxystilbenes as disclosed in the present specification (summarized, e.g., on page 2, lines 14-25).

Accordingly, in view of the generic disclosure in the prior art regarding the use of grape extract for cosmetic use and in view of the conflicting teachings of the prior art regarding glucosylated stilbenes, one skilled in the art would not have been motivated to select the claimed species of glucosylated hydroxystilbene, as the main active ingredient. Carson et al. worked only with resveratrol. Pezzuto et al. worked only with resveratrol as well, but mentioned two resveratrol glucosides. Teguo et al. provided evidence that the glucoside structure seriously impaired the anti-oxidant activity of hydroxystilbenes. The person of ordinary skill is an intensely practical person who is going to go where the art as a whole indicates he or she will have a reasonable likelihood of success. The art as a whole here does not motivate one of ordinary skill to glucosylated hydroxystilbenes, but rather to resveratrol itself. The

advantages found by applicants are what motivate toward the glucosylated hydroxystilbenes. All of applicants' claims are thus free of the obviousness rejection. Moreover, applicants' claims drawn to combating the signs of aging of the hair follicles are especially remote from the art.

From the foregoing, entry of the foregoing amendment and further and favorable consideration of the subject application on the merits are respectfully requested and such action is earnestly solicited.

Respectfully submitted,

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